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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Condensed 5-Membered Heterocyclic Compounds, Processes for Preparing Them and Pharmaceutical Compositions Containing These Compounds

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(30) (DE) P 43 04 650.9 1993/02/16

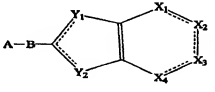
(57) 12 Claims

Notice: This application is as filed and may therefore contain an incomplete specification.

Abstract

Condensed five-membered heterocyclic compounds

The invention relates to condensed five-membered heterocyclic compounds of formula I:

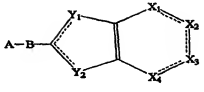


(I)

(wherein
R_a, R_b, X and Y are defined as in claim 1) and the isomers and salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases, which have valuable pharmacological properties, particularly aggregation-inhibiting effects, to pharmaceutical compositions containing the compounds and to processes for preparing them.

Claims

1. Compounds of formula I



(I)

(wherein

A denotes an aminoalkyl, amidino or guanidino group, at one of the nitrogen atoms whereof a hydrogen atom is optionally replaced by a hydroxy, alkyl, alkoxycarbonyl or phenylalkoxycarbonyl group,

or A denotes a piperidinyl group optionally substituted in the carbon skeleton by one or two alkyl groups or at the nitrogen atom by a group R_a and wherein a >CH- unit in the 4-position is optionally replaced by a nitrogen atom,

or A denotes an imidazolyl group,

or A denotes a pyridyl group which, if the heterocyclic group attached to AB- is a benzoxazole group, is bound to the group B other than via the 2-position;

R_a denotes a hydrogen atom or an alkyl, phenylalkyl, (C_{1-4}-alkoxy)carbonyl, or phenylalkoxycarbonyl group or an R_1-CO-(R_2CH)-O-CO- group (wherein R_1 denotes an alkyl group and R_2 denotes a hydrogen atom or an alkyl or phenyl group);

B denotes a straight-chain or branched C_{1-5}-alkylene group,

or an -alkylene-O-, -O-alkylene-, -alkylene-S-,

-S-alkylene-, -alkylene-NR_3-, -NR_3-alkylene-, -CO-NR_3- or -NR_3-CO- group (wherein R_3 denotes a hydrogen atom or an alkyl or phenylalkyl group),

or a cyclohexylene group,

or, if A denotes an optionally substituted piperidinyl group optionally with a >CH- unit in the 4-position replaced by a nitrogen atom,

or, if X_1 denotes a carbonyl group (with the proviso that, if -D-E-F denotes a 4-carboxy-butyl or 4-methoxy-carbonyl-butyl group, X_4 does not simultaneously denote an N-methyl-imino group),

or, if -D-E-F denotes a 2-carboxyethylaminocarbonyl or 2-methoxycarbonylethylaminocarbonyl group, and X_4 does not simultaneously denote a nitrogen atom,

then B may also denote a phenylene group optionally mono- or disubstituted in the phenyl nucleus by fluorine, chlorine or bromine atoms or by alkyl or alkoxy groups, whilst the substituents may be identical or different;

a first of the groups X_1, X_2, X_3 and X_4 denotes an F-E-D-C≤ or F-E-D-N< group (wherein

D denotes a straight-chain or branched C_{1-6}-alkylene group, a C_{2-6}-alkenylene group, an oxygen or sulphur atom, a CO-, SO-, SO_2-, CO-NR_3- or NR_3-CO- group or an SO_2NR_3- group bound to group E via the nitrogen atom,

E denotes a bond or a straight-chain or branched C_{1-5}-alkylene group, and

F denotes a carboxy, (C_{1-6}-alkoxy)carbonyl, phenylalkoxycarbonyl, (C_{3-7}-cycloalkyl)oxycarbonyl, (C_{3-7}-cycloalkyl)alkyloxycarbonyl, sulpho-, phosphono-, O-

alkyl-phosphono-, O,O-dialkyl-phosphono- or tetrazol-5-yl group);

a second of the groups X_1, X_2, X_3 and X_4 denotes a nitrogen atom or an R_b-C≤, R_c-N< or carbonyl group (wherein

R_b denotes a hydrogen, fluorine, chlorine or bromine atom or a C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, phenylC_{1-6}-alkoxy, amino, C_{1-6}-alkylamino or di(C_{1-6}-alkyl)amino group, and

R_c denotes a hydrogen atom, or a C_{1-6}-alkyl group optionally substituted by a hydroxy, alkoxy, amino, alkylamino, dialkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, pyrrolidino, piperidino, morpholino, piperazino or N-alkyl-piperazino group,

or R_c denotes a phenylC_{1-5}-alkyl group optionally mono- or disubstituted in the phenyl nucleus by fluorine, chlorine or bromine atoms or by alkyl or alkoxy groups, wherein the substituents may be identical or different);

and the remaining groups of the groups X_1, X_2, X_3 and X_4 each denote a nitrogen atom or an R_b-C≤ or carbonyl group whilst no more than two of the groups X_1, X_2, X_3 and X_4 denote carbonyl groups and at least one of the groups X_1, X_2, X_3 and X_4 denotes a carbonyl; FED-C≤ or R_b-C≤ group;

one of the groups Y_1 and Y_2 denotes a nitrogen atom or a methine group and the other group Y_1 or Y_2 denotes an oxygen atom or an R_d-N< group; and

R_d denotes a hydrogen atom, a C_{1-6}-alkyl group optionally substituted by a hydroxy, alkoxy, amino, alkylamino, dialkylamino, pyrrolidino, piperidino, morpholino, piperazino or N-alkyl-piperazino group,

or R_d denotes a phenylC_{1-5}-alkyl group optionally mono- or

disubstituted in the phenyl nucleus by fluorine, chlorine or bromine atoms or by alkyl or alkoxy groups, and the substituents may be identical or different,

or R_d denotes a C_{3-7}-cycloalkyl group,

or, if the groups R_c-N< and R_d-N< are bound to the same carbon atom, R_d together with R_c may denote a straight-chain or branched C_{2-5}-alkylene group;

wherein unless otherwise specified alkyl, alkylene and alkoxy moiety contains 1 to 3 carbon atoms)

and the isomers and salts thereof.

2. Compounds of formula I as claimed in claim 1, wherein:

A denotes an amidino group optionally substituted by a hydroxy or alkoxycarbonyl group,

or A denotes an aminoalkyl or benzyloxycarbonyl-aminoalkyl group,

or A denotes a piperidinyl group optionally alkyl-substituted in the carbon skeleton and optionally substituted by a group R_a at the nitrogen atom (wherein R_a denotes a hydrogen atom or an alkyl, benzyl, alkoxycarbonyl, benzyloxycarbonyl or R_1-CO-CH_2-O-CO- group (wherein R_1 denotes an alkyl group)) and wherein a >CH- unit in the 4-position may be replaced by a nitrogen atom,

or A denotes an imidazolyl group

or A denotes a pyridyl group which, if the heterocyclic group attached to AB- is a benzoxazole group, is bound to group B other than via the 2-position;

B denotes a straight-chain or branched C_{1-5}-alkylene group,

or an -alkylene-O-, -O-alkylene-, -alkylene-S-, -S-alkylene-, -alkylene-NR_3-, -NR_3-alkylene-, -CO-NR_3- or -NR_3-CO- group (wherein R_3 denotes a hydrogen atom or an alkyl group),

or a cyclohexylene group,

or, if A denotes an optionally substituted piperidinyl group optionally with a >CH- unit in the 4-position replaced by a nitrogen atom,

or, if X_1 denotes a carbonyl group (with the proviso that, if -D-E-F denotes a 4-carboxybutyl or 4-methoxycarbonylbutyl group, X_4 does not simultaneously denote an N-methyl-imino group),

or, if -D-E-F denotes a 2-carboxyethylaminocarbonyl or 2-methoxycarbonylethylamino carbonyl group and X_4 does not simultaneously represent a nitrogen atom,

then B may also denote a phenylene group;

a first of the groups X_1, X_2, X_3 and X_4 denotes an F-E-D-C< or F-E-D-N< group (wherein

D denotes a straight-chain or branched C_{1-6}-alkylene group, a C_{2-4}-alkenylene group, an oxygen or sulphur atom, a -CO-, -SO-, -SO_2-, -CO-NR_3- or -NR_3-CO- group or an -SO_2-NR_3- group bound to group E via the N atom (wherein R_3 is as hereinbefore defined),

E denotes a bond or a straight-chain or branched C_{1-5}-alkylene group, and

F denotes a carboxy, (C_{1-5}-alkoxy)carbonyl or (C_{5-7}-cycloalkoxy)carbonyl group);

a second of the groups X_1, X_2, X_3 and X_4 denotes a nitrogen atom or an R_b-C≤, R_c-N< or carbonyl group (wherein

R_b denotes a hydrogen, chlorine or bromine atom or an alkyl, hydroxy, alkoxy, amino, alkylamino or dialkylamino group, and

R_c denotes a hydrogen atom, or a C_{1-5}-alkyl group optionally substituted by a hydroxy, alkoxy, amino, alkylamino, dialkylamino, carboxy, alkoxycarbonyl, aminocarbonyl, pyrrolidino, piperidino, morpholino, piperazino or N-alkyl-piperazino group,

or R_c denotes a phenyl-C_{1-5}-alkyl group optionally mono- or disubstituted by alkoxy groups in the phenyl nucleus, wherein the substituents may be identical or different);

and the remaining groups of groups X_1, X_2, X_3 and X_4 each denote a nitrogen atom or an R_b-C≤ or carbonyl group (wherein R_b is as hereinbefore defined) whilst no more than two of the groups X_1, X_2, X_3 and X_4 denote carbonyl groups and at least one of the groups X_1, X_2, X_3 and X_4 denotes a carbonyl, FED-C≤ or R_b-C≤ group;

one of the groups Y_1 and Y_2 denotes a nitrogen atom and the other group Y_1 or Y_2 denotes an oxygen atom or an R_d-N< group; and

R_d denotes a hydrogen atom, or a C_{1-5}-alkyl group optionally substituted by a hydroxy, alkoxy, amino, alkylamino, dialkylamino, pyrrolidino, piperidino, morpholino, piperazino or N-alkyl-piperazino group,

or R_d denotes a phenylC_{1-5}-alkyl optionally mono- or disubstituted in the phenyl nucleus by alkoxy groups, and the substituents may be identical or different,

or R_d denotes a C_{3-6}-cycloalkyl group, or, if the groups

R_c-N< and R_d-N< are bound to the same carbon atom, R_d together with R_c may denote a straight-chain or branched C_{2-4}-alkylene group;

wherein unless otherwise specified each alkyl, alkylene and alkoxy moiety contains 1 to 3 carbon atoms;

and the isomers and salts thereof.

3. Compounds of formula I as claimed in claim 1, wherein:

A denotes an amidino group optionally substituted by a hydroxy or (C_{1-3}-alkoxy)carbonyl group,

or A denotes an aminoalkyl or benzyloxycarbonyl-aminoalkyl group,

or A denotes a piperidinyl group optionally methyl-substituted in the carbon skeleton and optionally substituted by a group R_e at the nitrogen atom (wherein R_e denotes a hydrogen atom or a methyl, benzyl, methoxycarbonyl, benzyloxycarbonyl or CH_3-CO-CH_2-O-CO- group) and wherein a >CH- unit in the 4-position may be replaced by a nitrogen atom,

or A denotes a 4-pyridyl or 1-imidazolyl group;

B denotes a straight-chain or branched C_{1-4}-alkylene group,

or an -alkylene-O-, -O-alkylene-, -alkylene-S-, -alkylene-NR_3-, -NR_3-alkylene- or -NR_3-CO- group (wherein each alkylene moiety contains 1 or 2 carbon atoms and the alkylene moiety of the alkylene-S- group and the nitrogen atom of the -NR_3-CO- group are linked to the group A, and wherein R_3 denotes a hydrogen atom or a methyl group),

or a 1,4-cyclohexylene group,

or, if A denotes an optionally substituted piperidinyl group optionally with a >CH- unit in the 4-position replaced by a nitrogen atom,

or, if X_1 denotes a carbonyl group (with the proviso that, if -D-E-F denotes a 4-carboxybutyl or 4-methoxycarbonyl-butyl group, X_4 does not simultaneously represent an N-methyl-imino group),

or, if -D-E-F denotes a 2-carboxyethylaminocarbonyl or 2-methoxycarbonylethylaminocarbonyl group, and X_4 does not simultaneously denote a nitrogen atom,

then B may also denote a phenylene group;

a first of the groups X_1, X_2, X_3 and X_4 denotes an F-E-D-C≤ or F-E-D-N< group (wherein

D denotes a straight-chain or branched C_{1-6}-alkylene group, a C_{2-4}-alkenylene group, an oxygen or sulphur atom, a -CO-, -SO-, $-SO_2-$, $-CO-NR_3-$ or $-NR_3-CO-$ group or an $-SO_2-NR_3-$ group bound to group E via the nitrogen atom (wherein R_3 is as hereinbefore defined),

E denotes a bond or a straight-chain or branched C_{1-4}-alkylene group, and

F denotes a carboxy, (C_{1-5}-alkoxy)carbonyl or cyclohexyloxycarbonyl group);

a second of groups X_1, X_2, X_3 and X_4 denotes a nitrogen atom or an $R_c-N<$, $R_c-C≤$ or carbonyl group (wherein

R_b denotes a hydrogen or chlorine atom or a hydroxy, methoxy, amino, methylamino or dimethylamino group, and

R_c denotes a hydrogen atom, or a C_{1-5}-alkyl group

optionally substituted by a methoxy, carboxy, methoxycarbonyl or aminocarbonyl group, or R_c denotes a phenylC_{1-5}-alkyl group);

and the remaining groups of groups X_1, X_2, X_3 and X_4 each denote a nitrogen atom, or an R_b-C≤ or carbonyl group (wherein R_b is as hereinbefore defined) whilst no more than two of the groups X_1, X_2, X_3 and X_4 denote carbonyl groups and at least one of the groups X_1, X_2, X_3 and X_4 denotes a carbonyl, FED-C≤ or R_b-C≤ group;

one of the groups Y_1 and Y_2 denotes a nitrogen atom and the other group Y_1 or Y_2 denotes an oxygen atom or an R_d-N< group; and

R_d denotes a hydrogen atom, or a C_{1-5}-alkyl group optionally substituted by a hydroxy, methoxy, amino, methylamino, dimethylamino, morpholino, piperazino or N-methyl-piperazino group,

or R_d denotes a phenylC_{1-5}-alkyl group optionally mono- or disubstituted by methoxy groups in the phenyl nucleus,

or R_d denotes a C_{3-6}-cycloalkyl group,

or, if the groups R_c-N< and R_d-N< are bound to the same carbon atom, R_d together with R_c may denote a straight-chain or branched C_{2-3}-alkylene group;

wherein unless otherwise specified each alkyl, alkylene and alkoxy moiety contains 1 to 3 carbon atoms;

and the isomers and salts thereof.

4. Compounds of formula I as claimed in claim 1, wherein:

A denotes an amidino, aminoC_{1-2}-alkyl or benzyloxycarbonylaminoC_{1-2}-alkyl group,

or a piperidin-4-yl group substituted by a group R_8 at the nitrogen atom (wherein R_8 denotes a hydrogen atom or a benzyl or benzyloxycarbonyl group);

B denotes a straight-chain or branched C_{1-4}-alkylene group,

or an -NH-CO- group the nitrogen atom whereof is linked to group A,

or B denotes a 1,4-cyclohexylene group,

or, if A denotes a substituted piperidin-4-yl group,

or, if X_1 denotes a carbonyl group (with the proviso that, if -D-E-F denotes a 4-carboxybutyl- or 4-methoxycarbonylbutyl group, X_4 does not simultaneously denote an N-methyl-imino group),

or, if -D-E-F denotes a 2-carboxyethylaminocarbonyl or 2-methoxycarbonylethylaminocarbonyl group and X_4 does not simultaneously denote a nitrogen atom,

then B may also denote a phenylene group;

a first of the groups X_1, X_2, X_3 and X_4 denotes an F-E-D-C≤ or F-E-D-N< group (wherein

D denotes a straight-chain or branched C_{1-4}-alkylene group, a C_{2-3}-alkenylene group or a -CO- group or a -CO-NH- group the nitrogen atom whereof is linked to the group E,

E denotes a bond or a straight-chain or branched C_{2-4}-alkylene group, and

F denotes a carboxy group or a (C_{1-4}-alkoxy)carbonyl group);

a second of the groups X_1, X_2, X_3 and X_4 denotes an R_c-N< or R_b-C≤ group (wherein R_b denotes a hydrogen or chlorine atom and R_c denotes a hydrogen atom or a methyl or ethyl group);

and the remaining groups of groups X_1, X_2, X_3 and X_4 each denote a nitrogen atom or an H-C≤ or carbonyl group;

one of the groups Y_1 and Y_2 denotes a nitrogen atom and the other group Y_1 or Y_2 denotes an R_d-N< group; and

R_d denotes a hydrogen atom or a C_{1-4}-alkyl group or R_d together with R_c denotes a straight-chain or branched C_{2-3}-alkylene group;

and the isomers and salts thereof.

5. Compounds of formula I as claimed in claim 1, wherein:

A denotes an amidino- or piperidin-4-yl group;

B denotes an ethylene group,

or, if A denotes a piperidin-4-yl group,

or, if X_1 denotes a carbonyl group (with the proviso that, if -D-E-F denotes a 4-carboxybutyl or 4-methoxycarbonylbutyl group, X_4 does not simultaneously represent an N-methyl-imino group),

or, if -D-E-F denotes a 2-carboxyethylaminocarbonyl or 2-methoxycarbonylethylaminocarbonyl group and X_4 does not simultaneously denote a nitrogen atom,

then B may also denote a phenylene group;

a first of the groups X_1, X_2, X_3 and X_4 denotes an F-E-D-C≤ or F-E-D-N< group (wherein

D denotes a straight-chain or branched C_{2-4}-alkylene group, an ethenylene group, or a -CO- group or a -CO-NH- group the nitrogen atom whereof is linked to the group E,

E denotes a bond or an ethylene group, and

F denotes a carboxy group or a (C_{1-4}-alkoxy)carbonyl group);

a second of the groups X_1, X_2, X_3 and X_4 denotes an R_c-N< or R_b-C≤ group (wherein R_b denotes a hydrogen or chlorine atom and R_c denotes a hydrogen atom or a methyl group);

and the remaining groups of groups X_1, X_2, X_3 and X_4 each denote a nitrogen atom or an H-C≤ or carbonyl group;

one of the groups Y_1 and Y_2 denotes a nitrogen atom and the other group Y_1 or Y_2 denotes an R_d-N< group; and

R_d denotes a methyl group or R_d together with R_c denotes an n-propylene group;

and the isomers and salts thereof.

6. A compound as claimed in claim 1 being:

(a) 5-[(2-carboxy-ethyl)-aminocarbonyl]-1-methyl-2-[2-(4-piperidinyl)-ethyl]-benzimidazole,

(b) 5-[(2-carboxy-ethyl)-aminocarbonyl]-1-methyl-2-[(4-piperidinyl)-aminocarbonyl]-benzimidazole,

(c) 5-(4-carboxy-1-oxo-butyl)-1-methyl-2-[2-(4-piperidinyl)-ethyl]-benzimidazole,

(d) 1-(4-carboxy-butyl)-3-methyl-8-[2-(4-piperidinyl)ethyl]-xanthine,

(e) 1-(4-carboxy-butyl)-3,9-dimethyl-8-[2-(4-piperidinyl)-ethyl]-xanthine,

(f) 2-(4-amidino-phenyl)-9-(4-carboxy-butyl)-8,10-dioxo-5,6-dihydro-4H,9H-pyrimido[1,2,3-cd]purine,

(g) 5-[(2-methoxycarbonyl-ethyl)-aminocarbonyl]-1-methyl-2-[2-(4-piperidinyl)-ethyl]-benzimidazole,

or a salt thereof.

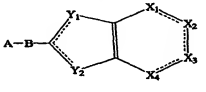
7. A compound as claimed in any one of claims 1 to 6 in the form of a physiologically acceptable addition salt with an inorganic or organic acid or base.

8. A pharmaceutical composition comprising a compound of formula I as claimed in any one of claims 1 to 6 or a physiologically acceptable salt thereof together with at least one physiologically acceptable carrier or excipient.

9. A process for preparing a compound as claimed in any one of claims 1 to 7, said process comprising at least one of the following steps:

a) (to prepare compounds of formula I wherein F denotes a carboxy group)

cleaving a protecting group from a compound of formula II



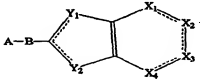
(II)

(wherein
A, B, X_1, X_2, X_3, X_4, Y_1 and Y_2 are defined as in any one

of claims 1 to 6, with the proviso that F denotes a (C_{1-6}-alkoxy)carbonyl, phenyl(C_{1-3}-alkoxy)carbonyl, (C_{3-7}-cycloalkyl)oxycarbonyl or (C_{5-7}-cycloalkyl)(C_{1-3}-alkyloxy)carbonyl group, or a carboxyl group protected by a cleavable group) by hydrolysis, hydrogenolysis or thermolysis;

b) (to prepare compounds of formula I wherein R_a denotes a hydrogen atom)

cleaving a protecting group from a compound of formula III

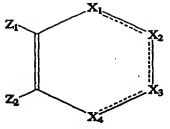


(III)

(wherein
A, B, X_1, X_2, X_3, X_4, Y_1 and Y_2 are defined as in any one of claims 1 to 6, with the proviso that R_a denotes a (C_{1-6}-alkoxy)carbonyl, phenyl(C_{1-3}-alkoxy)carbonyl, or R_1-CO-(R_2CH)-O-CO- group (wherein R_1 and R_2 are as hereinbefore defined), or a cleavable imino group protecting group) by hydrolysis, hydrogenolysis or thermolysis;

c) (to prepare compounds of formula I wherein one of the groups Y_1 and Y_2 denotes a nitrogen atom and the other group Y_1 or Y_2 denotes an R_d-N< group or, if the groups R_c-N< and R_d-N< are bound to the same carbon atom, R_c and R_d together may also denote a C_{2-5}-n-alkylene group)

cyclising a compound of formula IV

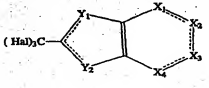


(IV)

(wherein
X_1, X_2, X_3 and X_4 are defined as in any one of claims 1 to 6, one of the groups Z_1 and Z_2 denotes an A-B-CO-NR_{d1}- group and the other group Z_1 or Z_2 denotes an HNR_{d2}- group, wherein A and B are defined as in any one of claims 1 to 6, one of the groups R_{d1} and R_{d2} denotes a hydrogen atom and the other group R_{d1} or R_{d2} has the meanings given for R_d in any one of claims 1 to 6), optionally formed in the reaction mixture, and subsequently, if desired, cleaving any protecting group used;

d) (to prepare compounds of formula I wherein B denotes an $-NR_3-CO-$ group)

reacting a compound of formula V



(V)

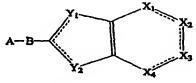
(wherein
X_1, X_2, X_3, X_4, Y_1 and Y_2 are defined as in any one of claims 1 to 6, and Hal denotes a chlorine, bromine or iodine atom) with a compound of formula VI

$$A' - HNR_3 \qquad \text{(VI)}$$

(wherein R_3 is defined as in any one of claims 1 to 6 and A' denotes a piperidinyl group optionally substituted in the carbon skeleton by one or two alkyl groups and at the nitrogen atom by a group R_a (wherein R_a is defined as in any one of claims 1 to 6 with the exception of the hydrogen atom) or denotes a cleavable imino group protecting group) and subsequently, if desired, cleaving any protecting group used;

e) (to prepare compounds of formula I, wherein F denotes a (C_{1-6}-alkoxy)carbonyl, phenyl(C_{1-3}-alkoxy)carbonyl, a (C_{3-7}cycloalkyl)oxycarbonyl or (C_{3-7}-cycloalkyl)(C_{1-3}-alkyloxy)carbonyl group)

reacting a compound of formula VII



(VII)

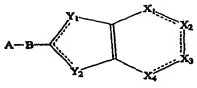
(wherein
A, B, X_1, X_2, X_3, X_4, Y_1 and Y_2 are defined as in any one of claims 1 to 6, with the proviso that F denotes a carboxy group or, if Z_3 denotes a hydroxy group, F may also represent an esterified carboxy group) with a compound of formula VIII

$$Z_3 - R_4 \qquad \text{(VIII)}$$

(wherein R_4 denotes a C_{1-6}-alkyl, a phenylC_{1-3}-alkyl, C_{3-7}-cycloalkyl or (C_{3-7}-cycloalkyl)C_{1-3}-alkyl group, and Z_3 denotes a hydroxy group or, if F denotes a carboxy group, Z_3 may also denote a nucleophilic leaving group);

f) (to prepare compounds of formula I wherein A denotes an amidino group optionally substituted at a nitrogen atom by a C_{1-3}-alkyl group)

reacting a compound of formula IX



(IX)

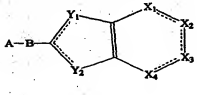
(wherein A, B, X_1, X_2, X_3, X_4, Y_1 and Y_2 are defined as in any one of claims 1 to 6, with the proviso that A denotes a Z_4-C(=NH)- group (wherein Z_4 denotes an amino, alkoxy, alkylthio, aralkoxy or aralkylthio group)), optionally formed in the reaction mixture, with an amine of formula X

$$R_5 - NH_2 \qquad (X)$$

(wherein R_5 denotes a hydrogen atom or a C_{1-3}-alkyl group) or an acid addition salt thereof;

g) (to prepare compounds of formula I wherein A denotes an amidino or guanidino group (substituted at one of the nitrogen atoms by a C_{1-3}-alkyl or (C_{1-3}-alkoxy)carbonyl group, or a piperidinyl group optionally substituted in the carbon skeleton by one or two alkyl groups and at the nitrogen atom by a group R_8 (wherein R_8 has the meanings given in any one of claims 1 to 6, with the exception of the hydrogen atom) and in which a >CH- unit in the 4-position may additionally be replaced by a nitrogen atom)

reacting a compound of formula XI



(XI)

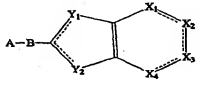
(wherein
A, B, X_1, X_2, X_3, X_4, Y_1 and Y_2 are defined as in any one of claims 1 to 6 with the proviso that A denotes an amidino or guanidino group or a piperidinyl group optionally substituted by one or two alkyl groups in the carbon skeleton and unsubstituted at the nitrogen atom and in which a >CH- unit in the 4-position is optionally replaced by a nitrogen atom) with a compound of formula XII

$$Z_5 - R_6 \qquad \text{(XII)}$$

(wherein
R_6 denotes a (C_{1-4}-alkoxy)carbonyl, C_{1-3}-alkyl, phenylC_{1-3}-alkyl or phenylC_{1-3}-alkoxycarbonyl group, or an R_1-CO-(R_2CH)-O-CO- group (wherein R_1 and R_2 are defined as in any one of claims 1 to 6), and Z_5 denotes a nucleophilic leaving group, or, if R_6 denotes an alkyl or phenylalkyl group, then Z_5, together with a hydrogen atom of the adjacent methylene group of the group R_6, may also denote an oxygen atom);

h) (to prepare compounds of formula I wherein D denotes a sulphinyl or sulphonyl group)

oxidising a compound of formula XIII



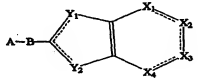
(XIII)

(wherein
A, B, X_1, X_2, X_3, X_4, Y_1 and Y_2 are defined as in any one of claims 1 to 6, with the proviso that D denotes a sulphur atom or a sulphinyl group);

i) (to prepare compounds of formula I wherein one of the

groups X_1 to X_4 denotes an F-E-D-N< group (wherein D is a straight-chain or branched C_{1-6}-alkyl group or a C_{2-6}-alkenyl group))

reacting a compound of formula XIV



(XIV)

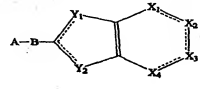
(wherein
A, B, Y_1, Y_2, X_1, X_2, X_3 and X_4 are defined as in any one of claims 1 to 6, with the proviso that one of the groups X_1 to X_4 denotes an H-N< group) with a compound of formula XV

$$Z_6 - D' - E - F \qquad (XV)$$

(wherein
E and F are defined as in any one of claims 1 to 6,
D' denotes a straight-chain or branched C_{1-6}-alkyl group or a C_{2-6}-alkenyl group and
Z_6 denotes a leaving group or, if D' contains a carbon-carbon double bond bound directly to the group F, Z_6 may also denote a hydrogen atom);

j) (to prepare compounds of formula I wherein D denotes a C_{2-6}-alkylene group)

hydrogenating a compound of formula XVI

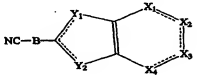


(XVI)

(wherein
A, B, Y_1, Y_2, X_1, X_2, X_3 and X_4 are defined as in any one of claims 1 to 6, with the proviso that D denotes a C_{2-6}-alkenylene group);

k) (to prepare compounds of formula I wherein A denotes a hydroxy-substituted amidino group)

reacting a compound of formula XVII

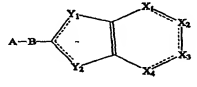


(XVII)

(wherein
B, Y_1, Y_2, X_1, X_2, X_3 and X_4 are defined as in any one of claims 1 to 6) with hydroxylamine or a salt thereof in the presence of a base;

l) (to prepare compounds of formula I wherein at least one of the groups X_1, X_2, X_3 and X_4 denotes a methine group)

dehalogenating a compound of formula XVIII



(XVIII)

(wherein
A, B, Y_1, Y_2, X_1, X_2, X_3 and X_4 are defined as in any one of claims 1 to 6, with the proviso that at least one of the groups X_1, X_2, X_3 and X_4 denotes a methine group substituted by a chlorine, bromine or iodine atom);

(m) (to prepare a compound of formula I wherein at least one of the groups X_1, X_2, X_3 and X_4 denotes a methine group substituted by a chlorine or bromine atom)

halogenating a compound of formula I wherein at least one of the groups X_1, X_2, X_3 and X_4 denotes a carbonyl group;

(n) performing the process of any one of steps (a) to (m) on a reagent having a protecting group and subsequently removing the protecting group used;

(o) converting a compound of formula I into a salt thereof; and

(p) resolving a compound of formula I into its isomers.

10. The use of a compound of formula I as claimed in any one of claims 1 to 6 or a physiologically acceptable salt thereof for the manufacture of a medicament for use in combatting bone degradation, tumours, metastases, thrombosis or aggregation-related conditions.

11. A method of treatment of the human or non-human animal body to combat bone degradation, tumours, metastases, thrombosis or aggregation-related conditions, said method comprising administering to said body a compound of formula I as claimed in any one of claims 1 to 6 or a physiologically acceptable salt thereof.

12. Each and every novel compound, composition, process, method and use herein disclosed.

SUBSTITUTE

REMPLACEMENT

SECTION is not Present

Cette Section est Absente